Amendments to the Specification

Please replace the paragraph at page 1, lines 6-7 with the following replacement paragraph:

~~The present application claims the benefit of priority from a provisional application filed June 8, 2001 and having a U.S. Serial No. 60/297,089.~~

The present application is a divisional application of, and claims benefit of U.S. Patent Application Serial No. 10/165,422, filed June 7, 2002, entitled "Antithrombotic thrombin variants," now issued as U.S. Pat. No. 6,706,512, which itself claims benefit of priority from U.S. Provisional Application Serial No. 60/297,089, filed June 8, 2001, the disclosure of which is hereby incorporated herein in its entirety by reference.

Please replace the paragraph at page 18, lines 6-20 with the following replacement paragraph:

The terms "percent sequence identity" or "percent sequence similarity" as used herein refer to the degree of sequence identity between two sequences as determined using the algorithm of Karlin & Attschul (1990) Proc. Natl. Acad. Sci. 87: 2264-2268, modified as in Karlin & Attschul (1993) Proc. Natl. Acad. Sci. 90: 5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Attschul et al. (1990) T. Mol. Biol. Q15: 403-410. BLAST nucleotide searches are performed with the NBLAST program, score=100, wordlength=12, to obtain nucleotide sequences homologous to a nucleic acid molecule of the invention. BLAST protein searches are performed with the XBLAST program, score=50, wordlength=3, to obtain amino acid sequences homologous to a reference polypeptide. To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in *Attschul et al.* (1997) Nuc. Acids Res. 25: 3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g. XBLAST and NBLAST) are used. ~~See http://www.ncbi.nlm.nih.gov.~~

Please replace the paragraph from page 27, lines 19-30 to page 28, lines 1-3 with the following replacement paragraph:

Another aspect, therefore, of the present invention provides a double mutant variant prothrombin or thrombin, WE, that has alanine substitutions both at the W215 and E217 positions. The amino acid sequence SEQ ID NO: 3 of the thrombin variant W215A/E217A is shown in Fig. 3, and that of the cleaved and enzymically active thrombin variant WE B-chain (SEQ ID NO: 4) is given in Fig. 4. As with the W215A variant thrombin (SEQ ID NO: 1), the amino acid substitution were introduced into an isolated nucleic acid encoding the thrombin protein by PCR-based mutagenesis, as described in Example 1, below. The sequence of the thrombin-encoding nucleic acid (SEQ ID NO: 5) ~~(GenBank Accession No._____)~~, having the W215A and E217A substitutions, is shown in Fig. 5. The sequence of the WE B-chain thrombin-encoding nucleic acid (SEQ ID NO: 12), having the W215A and E217A substitutions, is shown in Fig. 14. X-ray crystallgraphic data showing the orientation of the alanine substitutions in the double mutant W215A/E217A (WE) around the binding site of PPACK is shown in Fig. 6.

Please replace the paragraph at page 38, lines 20-23 with the following replacement paragraph:

In another embodiment of the variant thrombins of the present invention, the variant thrombin having the W215A and E217A substitutions is encoded by a nucleic acid comprising an amino acid sequence selected from SEQ ID NO: 5 and SEQ ID NO:6 ~~(GenBank Accession No._____)~~.

Please replace the paragraphs from page 56, lines 6-30 to page 57, lines 1-11 with the following replacement paragraphs:

The antihemostatic effects of the antithrombotic enzymes were assessed following injection of 0.1, 0.2 or 0.45 mg/kg (1.8, 3.6 or 8 nmoles/kg) of APC or 0.011, 0.022, 0.055, 0.11 or 0.22 mg/kg (0.3, 0.6, 1.5, 3 or 6 nmoles/kg) of WE. Blood was drawn from the AV shunt, or by standard venepuncture in the high-dose WE studies when no thrombogenic shunt was inserted distal to the shunt. The total volume of blood drawn for all *in vitro* measurements was restricted to less than 10 mL per day in each study subject. Blood samples (0.45 or 0.9 mL) were drawn into 3.2% trisodium citrate at regular intervals for at least 100 mins. from time 0 (dosing) for immediate assessment of hemostasis by using point-of-care APTT testing. Samples were

processed rapidly and all APTT measurements were performed between 5 and 7 mins. after blood drawing. When the APTT value was significantly prolonged, the APTT test was repeated several times on the same sample for up to 100 mins. at random intervals.

[[ ]]

Both WE and APC treatments compromised coagulation-dependent hemostasis at all doses administered, as reflected by significant systemic anticoagulation by the time of the first blood sampling 10 mins. after dosing, as shown in Fig. 9. APTT values returned to pre-treatment baseline after APC ($p>0.86$ for each), but not after treatment with WE doses of 0.022 mg/kg or more ($p<0.03$ for each) by the end of the 100 mins. observation period. The prolongation of APTT 10 and 40 mins. after injection of WE indicated secondary anticoagulant dose response (R^2 =0.89 and 0.93, respectively). The anticoagulant effect was disappearing from blood samples and APTT values approached those of the pre-dosing samples at comparable rates during *ex vivo* during incubation of citrated blood samples taken after either APC or WE treatments, as shown in Example 9, below, and Fig. 10.